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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/574,645	SALOMON ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-14 and 17-26* is/are pending in the application.

4a) Of the above claim(s) *7-14 and 21-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

This action is in response to paper filed 10/5/2009.

Claims 1, 7-14, 17-26 are pending.

Claims 7-14, 21-26 are withdrawn from consideration.

Claims 1, 17-20 are being examined.

Priority

1. The instant application was filed 8/10/2006 and is a national stage entry of PCT/US04/432649 filed 10/1/2004.

Election/Restrictions

2. This application contains claims 7-14, 21-24 drawn to an invention nonelected with traverse in the reply filed on 9/24/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method of detecting NeuroAIDS disease in macaque or human comprising assaying the expression level of a SEQ ID NO 1 in the central nervous system of the macaque or human wherein 2.5 over expression of SEQ ID NO 1 relative to expression of SEQ ID NO 1 in an uninfected central nervous system control sample from another macaque, if the detection is in a macaque, or human, if the detection is in a human..

It is noted that applicant elected overexpression of human Cripto-1, which is SEQ ID NO 1 of the instant claims.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches in example 2 a study of 5 pig tailed Macaque. The study compares the expression of RNA isolated from the parietal cortex of 1 control uninfected Macaque with expression from 4 macaque infected with SHIV by use of human cytokine cDNA array (see paragraph 0073). The specification further teaches, "A more stringent 2.5 difference was chosen as an arbitrary cutoff value for differences in gene expression." (See paragraph 0073). The specification further teaches the relative expression was calculated by use of normalization spots and standard housekeeping genes.

The specification teaches in Table 2 there was a 9.56 fold increase in Tetracarcinoma-derived growth factor (Cripto-1) in the cerebral cortex of exsanguinated 4 SHIV infected macaque relative to the uninfected macaque.

The specification teaches, "The function of Cripto in neurons in the adult brain and its up regulation in the brains of SHIV-infected macaques are also unknown" (see paragraph 0086).

Presence and absence of working examples

The specification teaches a single study involving 4 SHIV infected macaque and 1 non-infected control in which macaque homologs of nucleic acid that hybridize to SEQ ID NO 1 reagents are up regulated. However, this study uses a single control that has not been infected with any virus. Further this study examines tissue that has been

collected post-exsanguinations and thus altered expression may merely be differences in the handling of the one control sample. This study does not teach detection of SEQ ID NO 1, but the macaque homologue of SEQ ID NO 1.

The specification does not teach any working examples of diagnosis based on detection or over expression of SEQ ID NO 1. The studies of the specification are drawn to detection of the macaque homologue of SEQ ID NO 1. The specification does not teach detection of SEQ ID NO 1, but the use of a human cDNA array and primers to the cripto-1 human sequence to detect the macaque homolog of SEQ ID NO 1, which is different than SEQ ID No 1 as discussed in the state of the art section below.

The specification does not teach any studies in humans.

The state of prior art and the predictability or unpredictability of the art:

Sequence analysis by blast (blast.ncbi.nlm.nih.gov/Blast.cgi, 9/4/2008, pages 1-32) teaches that SEQ ID NO 1 is not the macaque cripto gene but has regions of 95% identity, but numerous gaps and regions with as little as 76% identity. Thus the BLAST analysis teaches that SEQ ID No 1 is not the macaque Cripto-1 gene and presumably was not being detected in the macaque models. Thus it would be unpredictable to associate the expression of a SEQ ID NO 1 with detection of a NeuroAIDS as the specification does not teach detection of SEQ ID NO 1, but amplification of a macaque homolog that is amplified by primers to a fragment of the human cripto-1 gene or genes that hybridize to a probe for the human Cripto-1 cDNA.

Caceres et al (proceedings of the National Academy of Sciences (2003) volume 100, pages 13030-13035) teaches "we have identified 169 genes that exhibited

expression differences between human and chimpanzee cortex, and 91 were ascribed to the human lineage using macaques as an outgroup" (abstract). Caceres teaches examination of 290 genes that differed between chimpanzees and humans 221 showed a human specific pattern of hybridization and 211 of the 221 had greater intensity in human samples (13033, 1st column). Carceres further teaches that there is a higher degree of divergence between human and rhesus sequence, thus making interpretation of microarray data less reliable (13033, 2nd column).

Roberts et al (American Journal of Pathology (2003) volume 162, pages 2041-2057) teaches a study to examine differential regulation of gene expression in macaques' brains by SIV infection. Roberts teaches 98 genes were identified, with 66 genes up regulated in the occipital lobe, 68 up regulated in the midbrain and 19 in the cerebellum (2047, 2nd column). Roberts teaches in table 2, 98 genes up regulated and does not identify SEQ ID NO 1. Roberts further notes that gene regulation is appears to dependent on the location of the neurons relative to the infection (2055, 2nd column). Thus Roberts did not find the SEQ ID NO 1 was up regulated in macaque models of NeuroAIDS and further noted that gene expression patterns are dependent on the location from which the sample is take.

It is relevant to point out that the art of Cheung et al (Nature Genetics (2003), volume 33 pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last

paragraph; Fig 1). The data indicates that, for example, expression of *ACTG2* in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a phenotype.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology (2001) volume 195, pages 53-65). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion).

Benner et al (Trends in Genetics (2001) volume 17, pages 414-418) teaches that, "Here, the 'homology-implies-equivalency' assumption is restricted to a subset of homologs that diverged in the most-recent common ancestor of the species sharing the homologs. This strategy is useful, of course. But it is likely to be far less general than is widely thought. Two species living in the same space, almost by axiom, cannot have identical strategies for survival. This, in turn, implies that two orthologous proteins might

not contribute to fitness in exactly the same way in two species" (see page 414, 3rd column last full paragraph). Benner specifically describes that although the leptin gene homologs have been found in mice and humans, their affect is different (see page 414, 3rd column last paragraph-3rd column page 415). Benner specifically teaches that the leptin gene in mice plays a major role in obesity, but no such effect has been demonstrated in humans due perhaps to the different evolutionary forces. Benner thus teaches that the activity and function of genes in different species is unpredictable.

Raghavan et al (Brain Pathology (1997) volume 7, pages 851-861) teaches a comparison of SHIV infection on pig tailed macaque compared to rhesus macaque. Raghavan teaches, "Our data show a clear contrast in the neuropathogenesis of SHIV infection in pig-tailed and rhesus macaque (page 858, 2nd column, 1st paragraph). Raghavan teaches that the pig tailed macaque the virus failed to become active, while in the rhesus macaque there was lentiviral replication which was accompanied by brain legions (page 858, 2nd column). Thus it would be unpredictable to correlate the expression of a gene in one species of macaque with any other mammal when Raghavan teaches the SHIV has different affects on two members of the macaque family and is thus unpredictable in macaques. Raghavan teaches the SHIV infection differed from the SIV infection of the brain as SHIV infected macaques lacked meningeal inflammation that is observed in SIV. Raghavan suggests the SIV and SHIV induced NeuroAIDS have different pathologies. Thus it would be unpredictable to associate a finding based on one virus known to cause NeuroAIDS, when Raghavan teaches these are differences in responses.

Further, Enard et al (Science (2002) volume 296, pages 340-343) teaches that intraspecies variation in gene expression in brain tissue is substantial (page 340, 3rd column). Enard continues, "One human brain sample differs more from the other human samples than the latter differ from the chimpanzee samples. However, for both the brain and liver samples, the humans, as well as the chimpanzees, fall into two mutually exclusive groups when their gene expression patterns are related to that seen in the orangutan, which is evolutionarily further, removed from humans and chimpanzees than these are from each other." Thus it would be unpredictable in view of Enard to extrapolate the teachings based on a single control in one species due to the intraspecies variability in gene expression in brain, but it would be further be unpredictable to do such extrapolation to other mammals, as there is great variability between primates as demonstrated by differences between orangutan, chimpanzees, and humans. Further comparison of chimpanzees to human and macaque resulted in a 5.5 fold difference in expression. Thus it would be unpredictable to extrapolate the findings of a single finding using a single macaque as a control when the art teaches there is substantial intraspecies variation and suggests it would further be unpredictable to make interspecies comparison based on the teachings of Enard.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed one of skill in the art would first have to determine if a predictive relationship over expression of SEQ ID NO 1 in the central

nervous system of a macaque or human relative to a sample from the uninfected nervous system of another mammal of the same species. This would be unpredictable as the specification teaches a single study of 4 macaques infected with SHIV compared to a single control that was not infected. A single experiment with such a small size sample cannot be reasonably extrapolated to any macaque or human, as discussed further below. First the specification used primers and /or probes to human cripto-1, which is SEQ ID No 1, however the studies were done in macaque and would not have detected SEQ ID NO 1, but the macaque homolog, which is quite different as demonstrated by the BLAST alignment. Further the expression of the cripto-1 homolog may be a result of the viral infection, exsanguinations, or handling of the sample as gene expression in general is variable and the specification teaches macaque are out bred models, suggesting greater variability in gene expression patterns.

Further practicing the invention as claimed would require undue trial and error experimentation as the claims are drawn to "any" central nervous system tissue. The teachings of Roberts demonstrate that the different regions of the macaque brain have differential expression patterns based on anatomical location and suggest that this expression is due to proximity to active infection. Thus based on the teachings of Roberts it would be unpredictable to extrapolate the findings of the instant specification in that the macaque homologue of SEQ ID NO1 is up regulated in the cortex of macaque as diagnostic in any other central nervous system tissue without specific evidence due to this variability.

Further the skilled artisan would have to determine if "2.5 fold overexpression" is required to result in a predictable association of SEQ ID NO 1 over expression and NeuroAids. This would be unpredictable as the specification teaches a single study with 1 control and 4 infected macaque. Cheung teaches that there is a 17 fold natural gene variation among individuals, thus the teachings of Cheung suggests the non-treated macaque may simply be an outlier.

In view of teachings of the art as to the variability of expression data as a whole, the limited population studied, and the use of a single control, the skilled artisan would have to undertake unpredictable and undue trial and error experimentation to determine if such a relationship exists in mammals. This would be unpredictable as in the single study taught by the specification SEQ ID NO 1 was not detected, but macaque homologs that hybridize to reagents for SEQ ID NO 1.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

It is noted that that the instant claims are drawn to the detection of NeuroAids by detecting a 2.5 fold increase in SEQ ID NO 1 in sample from the central nervous system of a macaque or human by comparison to an uninfected central nervous system control of a macaque or human depending on the species being analyzed. It is noted that SEQ

ID NO 1 is the human cripto1 gene and the only experiments done in the specification were done in macaque and thus the specification provides no studies in which SEQ ID NO 1 is detected.

The response begins on page 5 by a brief review of the enablement rejection. On page 6, the response notes that the examiner has withdrawn the aspects of the rejection drawn to the normalization of expression.

The response on page 6 beings the arguments with respect to sample size and infection. The response continues by presenting MPEP2164.05(a). The response then asserts that one of skill in the art at the time would have been concerned with the study of NeuroAIDS. The response continues by asserting that one of skill in the art would have recognized macaque as an acceptable model of NeuroAIDS in humans and further alleges that the model overcomes obstacles of performing NeuroAIDS studies in humans. The response continues by noting that the study of the instant specification has been published as Stephens et al Neuroscience Lett (2006) volume 410, pages 94-99). The response continues by asserting that as Stephens is post-filing art, this demonstrates that one of skill in the art would find a single control animal as acceptable. These arguments have been thoroughly reviewed but are not considered persuasive as Stephens does not the up regulation of the macaque homolog of cripto1 allows for detection or diagnosis of NeuroAids. Stephens is presenting an experimental observation in a study of only Macaque and does not teach that the increased in diagnostic of NeuroAIDS in Macaque or humans as claimed. Further the teachings of Stephens in figure 2 demonstrate that there is variability in gene expression in different

regions of central nervous system thus demonstrating that comparison of macaque cripto1 homologue expression in any central nervous system in not predictable for comparison to expression in any other tissue. Thus while the peer reviewed publication of Stephens teaches the skilled artisan would view findings as interesting and worthy of publication the teachings of Stephens does not specifically demonstrate that one of skill in the art would consider the increased expression of SEQ ID NO 1 as able to predictably detect NeuroAIDS in humans and Macaque.

The response then presents arguments to the control animals not being infected and continuing by asserting the examiner has taken the position that a virus alone may induce gene expression. The response continues by noting that Roberts teaches that the control macaques were not infected. The examiner concurs that Roberts teaches the use of macaque that have not been infected. However, Roberts also teaches the use of RNA from the frontal lobe of 6 infected and 6 control macaque. Thus Roberts teaches that the use of multiple controls is art accepted.

The response on page 9 continues by noting that the examiner has presented the teachings of Roberts and Buch as studies that suggest unpredictability of SEQ ID No 1 in the detection of NeuroAIDS. The response continues by again noting the examiner has withdrawn arguments to Wu, Newton and Vandesompele. The response continues by asserting microarray studies are an effective way of analyzing up regulation of Cripto-1. These arguments have been thoroughly reviewed but are not considered persuasive as the claims are drawn to detection of SEQ ID NO 1, which is the human cripto1 sequence. The instant specification does not teach detection of SEQ

ID NO 1, but a macaque homologue or other nucleic acid that hybridizes to probes fro SEQ ID NO 1 and thus is not enabling for detecting neuroaids by detection of SEQ ID NO 1.

The response continues by asserting the Roberts paper actually supports the instant application. The response continues by asserting that the microarray study of Chismar (Biotechniques (2002) volume 33, pages 516-522) are from the same lab as they have several authors that are the same. These are arguments of counsel that have not been supported by evidence. There is no evidence that the Roberts and Chismar papers are from the same lab, although they do have two of the same authors.

The response continues by asserting that Chismar teaches the use of macaque models to report on human health and disease was accepted and the macaque cripto-1 in Macaque NeuroAids would reliably report up regulation of SEQ ID NO 1 in human Neuroaids. These arguments have been thoroughly reviewed but are not considered persuasive as the teachings of Chismar do not specifically teach of recite cripto1 or SEQ ID NO 1 for the detection (diagnosis) of NeuroAIDS.

The response continues Chismar demonstrates that cross-species hybridization is an acceptable method for analysis. The response continues that the instant application uses a Clontech array, not the Affymetrix array used by Roberts/Chismar. The response continues by noting that Chismar teaches, " Thus, caution is necessary in interpreting data from genes called as negative or marginal, as important transcript abundance information may be missed if gene calls are arbitrarily excluded based on this criterion." It is noted that the section of Chismar quoted is normalization and

transcript detection and thus the calling is the detection of a transcript, not up regulation as asserted in the response. The response continues that Chismar advocates a confirmation study should be done if no up regulation is found. These arguments have been thoroughly reviewed but are not considered persuasive as Chismar teachings are drawn to the predictability of detecting the expression of a gene and not the level of expression across species (abstract). Further, Chismar teaches confirmation should be done for negative or marginal determinations of calling. Thus while Chismar suggest that a human array can be used to detect gene expression in macaque, Chismar does not teach that the level of expression detected in macaque is the same in similar disease states between humans and macaque. Further, Chismar provides no evidence that macaque cripto-1 is the only sequence that hybridizes to the probes of the Clontech array used by applicants.

The response continues by noting that Roberts did not confirm the Cripto-1 expression by PCR as suggested by Chismar. These arguments have been thoroughly reviewed but are not considered persuasive as the section of Chismar relied upon is directed to discussing "the calling " or detecting the presence of a transcript, not the level of up regulation the response is asserting.

The response continues by noting again the instant application has identified the up regulation of cripto-1 by use of the Clontech array and has validated it by PCR as suggested by Chismar. As addressed above Chismar does not specifically suggest confirmation or up regulation by PCR, but missed calling, which is different. Further, the claims are drawn to detection of SEQ ID NO 1, which is not present in Macaque.

Further the inability of Roberts using an Affymetirx microarray to replicate the instant findings with a Clontech microarray suggest any method of detecting SEQ ID NO 1, a homologue, or other nucleic acids that hybridize to the probes is unpredictable as a 9.5 fold increase should be detectable by the methods of Roberts as Chismar teaches the genes with the highest signal intensity have the highest call rate.

The response concludes by asserting that the lab group which published Roberts admits no observance of up regulation of gene may be a false negative. These again are arguments of counsel that have not been substantiated by evidence as there is no evidence that the Chismar and Roberts are the same labs. Further the teachings of Chismar are drawn to call rates, not the level of expression. Thus a false call rate does not implicate a lack of up regulation as asserted. Further Chismar teaches the teachings of Roberts are in preparation (516, 3rd column. 1st paragraph), thus suggesting that Roberts knew the teachings of Chismar and would have taken the knowledge of Chismar into account for the analysis of data.

The response notes that Buch and Siu teach the analysis based on the Affymetrix array and asserts differences in the Affymetirx array and the Clontech array of applicant may not necessarily result in detection of cripto1. These arguments have been thoroughly reviewed but are not considered persuasive Siu teaches that it used the same human cytokine array from Clontech as the instant specification (page 231, 1st column). Further the teachings of Siu did replicate the increased expression of leukocyte interferon inducible peptide, thus suggesting that gene expression may be

reproducible by another lab using the same microarray could not detect the 9.56 fold up regulation of nucleic acids that hybridize to probes for human cripto1.

The response again asserts that Buch and Siu that Macaque are acceptable models of human NeuroAIDS. These arguments have been thoroughly reviewed but are not considered persuasive as the Buch and Siu present no evidence that up regulation of human cripto-1, SEQ ID NO 1, or probes that hybridize to human cripto-1 are diagnostic of NeuroAIDS. The indication that a model is valuable in studying a disease does not indicate that the information gleaned from the study are indicative of disease diagnosis in another species, as evidenced by the teachings of Benner which teaches gene homologues in different species have different functions due to different evolutionary pressures.

The response continues to allege the examiner continues arguing the unpredictability of post-exsanguinations collection of tissue for gene expression analysis. The examiner has previous withdrawn these arguments and thus they are moot.

The response on page 12 then moves to arguments to detection of the SEQ ID NO 1. The response correctly notes that the office action contends that the specification does not teach detection of SEQ ID NO 1, but something that hybridizes to probes in the Clontech cytokine microarray. The response continues by asserting that one of ordinary skill in the would have recognized the methods detection of NeuroAIDS. This is arguments of counsel that have not been substantiated by evidenced. There is no evidence of record other than the assertions of the response to demonstrate the

detection of SEQ ID NO 1 is up regulated in human NeuroAIDS. Further the reliance of the instant response on the difference in detection by Clontech and Affymetrix arrays of a macaque sequence that hybridizes to probes for human cripto1 further demonstrate this argument.

The response asserts that continues by asserting that one of skill in the would recognize that the up regulation of macaque Cripto-1 in macaque NeuroAIDS is reliable in detecting human cripto-1 (SEQ ID NO 1) in human NeuroAIDS. The response then contends that the declaration of Berman and Roberts was an acceptable animal model for studying NeuroAIDS in humans. First, Berman and Roberts do not support the assertion that macaque models can be used to diagnose human NeuroAIDs, but merely indicate it is a good model to study neuroaids. The examiner agrees that it is a suitable model for studying NeuroAIDS, however the claims are drawn to the detection (or diagnosis) of NeuroAIDS in a human or macaque. The response continues by quoting sections of Chisma and Roberts to support the position. Again, the examiner agrees the importance of these studies however, none of the recited sections demonstrate that the nucleic acid detected by the method of the instant disclosure is SEQ ID NO 1 as required by the instant claims or is predictably applicable to human subjects.

The response continues by noting that the Berman declaration teaches that human primers were used in the instant application. These arguments have been thoroughly reviewed but are not considered persuasive as the claims are drawn to detection of SEQ ID NO 1, not sequences that can be amplified by the primers of SEQ ID NO 3 and SEQ ID NO 4.

Further the teachings of Benner demonstrate that gene homologs from different species often have different functions. Thus the mere assertion that a gene upregulated in one species is correlated with a disease cannot be viewed as a nexus to diagnose a disease in another species without specific evidence that the gene has the same function in another species.

The response again concludes it's assertion by again arguing that macaque NeuroAIDS is a model of human Neuroaids and the use of human primers is an accepted method to determine up regulation of macaque genes and that the findings In macaque NeuroAIDS indicates that cripto1 is upregulated in human NeuroAIDS.

As stated in the MPEP, 2106 "Arguments of Counsel"

"However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37

CFR 1.195, or
(iii) under 37 CFR 1.129(a).

The response has provided no evidence to support the arguments that over expression of a macaque nucleic acid sequence that hybridizes with probes to SEQ ID NO 1 are indicative of SEQ ID NO 1 being over expressed in macaque or human neuroaids. The specification and arguments have provide no evidence that SEQ ID NO 1 is over expressed in human or macaque neuroaids. The specification has merely provided evidence that a sequence that hybridize to probes in a single assay revealed an increase in a message presumed to be cripto1. The art of Sui using the same array and methods did not replicate this finding although replicating increased expression of the leukocyte interferon inducible peptide. The assertion that the use of human primers can be used to amplify macaque is beyond the scope of the claimed invention as claim 1 requires detection of SEQ ID NO 1, which is not present in macaque as evidenced by the blast analysis. Finally the arguments with respect to detection of SEQ ID NO 1 in humans being indicative of NeuroAIDS in humans has not been supported by evidence and would be unpredictable at least due to the teachings of Benner.

The response then alleges SHIV infection is a model of human NeuroAIDS. These arguments have been previously addressed and are not persuasive for the reasons of record.

The response then quotes Williams page 295 which indicate that SHIV infection is a model system for NeuroAIDS. The examiner agrees that SHIV is a model system for NeuroAIDS in rhesus macaque, however Williams continues by stating, "

Examination of archival tissues from macaques infected with SHIVKU–2 showed that of 14 infected rhesus macaques that developed AIDS, 10 had neuropathological changes with clear evidence of virus replication in macrophages in the brain. In contrast, of 22 infected pig-tailed macaques that developed AIDS, 21 had no evidence of SHIVKU–2 replication in the brain. This difference in susceptibility to CNS disease caused by SHIVKU–2 in the two macaque species provides a novel system to further explore mechanisms of lentiviral neuropathogenesis" (page 295, 2nd column, last paragraph). Thus according to the Williams article provided by applicant to support their position SHIV constructs similar to those used in the instant application demonstrated no neural replication in pig tailed macaque, but did in rhesus macaque. The instant application describes studies in pig tailed macaque. Thus the teachings of Williams, while suggesting the importance of the macaque models demonstrates that one of skill in the art can not predictably extrapolate the teachings of one macaque species (rhesus) to another macaque (pig tailed) as they are differently affected by SHIV infection. Thus it would be unpredictable to practice the invention as claimed in "any" macaque or human.

The response then asserts, "A closer analysis of Buch also reveals that this reference supports the Applicants and not the Examiner. Buch does state that HIV and SHIV use different receptors for infection, CCR5 (R5) and CXCR4 (X4) receptors, respectively, as pointed out by the Examiner. However, again, one of ordinary skill in the art recognized that, even with these differences, macaque/SHIV was the best model system (as discussed above), and this system was recognized by ordinary artisans as indicative of human NeuroAIDS (e.g., see the Berman declaration at ¶ 10)." The

response then continues by providing other sections of Buch. The examiner still concurs that SHIV is a model of NeuroAIDS, but the teachings of Buch indicate "no pathological changes were observed in these brains" (page 73, 1st column, 1st full paragraph) and that the studies were done in rhesus macaque which have neuropathological consequences of SHIV infection according to Williams, while the pig tailed macaque do not have viral reproduction according to Williams.

The response then asserts, "Stephens does state, as noted by the Examiner, "Whether cripto-1 expression is elevated during the course of neurosis due to enhanced expression of one or more cytokines/chemokines remains to be determined." (Stephens at pages 97-98, bridging paragraph, final sentence.) Again, as stated above, enablement relates to what one of ordinary skill in the art would have accepted. The Examiner appears to suggest that Cripto-1 up regulation may be observed with abnormalities in cytokine/chemokine expression independent of HIV/SHIV infection. However, Sui states, "Human immunodeficiency virus (HIV)-encephalitis results from a cascade of viral-host interactions that lead to cytokine and chemokine imbalance, which then leads to neuropathologic manifestations of the disease." (Sui at first sentence of the abstract). Thus, the manifestations of human NeuroAIDS itself is caused by cytokine/chemokine imbalance. Also, just as discussed above how ordinary artisans did not infect controls with any virus at all, one of ordinary skill in the art would have recognized that regardless of the identification of the identity of the molecule(s) that directly allow(s) for/produce(s) up regulation of Cripto-1, the up regulation of Cripto-1 indicates the presence of NeuroAIDS. As a simple analogy, a high level of blood

glucose is indicative of diabetes; however, whether that diabetes is Type I (failure to produce insulin) or Type 2 (insulin resistance) can not be determined simply by measuring the blood glucose levels, even though a diagnosis of diabetes may still be made. Here, although it is not known what molecules interact to cause up regulation of Cripto-1 in NeuroAIDS, Cripto-1 is still indeed upregulated during NeuroAIDS. Therefore, one of ordinary skill in the art would have recognized that Cripto-1 up regulation is indicative of NeuroAIDS, even if the underlying mechanism was not known." These arguments have been thoroughly reviewed but are not considered persuasive as Stephens does not teach that SEQ ID NO 1 was detected in macaque, but at best a homologue is detected. How, or why the expression is increased is beyond the scope of the claimed invention. The fact that the macaque cripto 1 gene does not comprise the sequence of SEQ ID NO 1, indicates the specification is not enabling for detection of SEQ ID NO 1 for detection of NeuroAIDS. Further as stated previously Stephens does not teach detection of SEQ ID NO 1 in a human central nervous system sample is indicative of NeuroAIDS.

The response asserts, "In regards to determining what level of over expression indicates a disease state, again, it is what one of ordinary skill in the art would have recognized as indicating the disease state. One of ordinary skill in the art would have recognized that the sample size used in the instant specification was acceptable, as detailed above. Further, as discussed in detail below, one of ordinary skill in the art would have recognized that the variations among individuals and species exist but that the studies used in the instant specification were acceptable to report on conditions of

human NeuroAIDS generally. The 2.5-fold difference, as indicated by the specification as filed at ¶ [0073], was an arbitrary cut-off value for the microarray experiments. However, the exact level of over expression of Cripto-1 need not be claimed. As discussed above, the Applicants performed RT-PCR experiments which showed that Cripto-1 was indeed upregulated, confirming the results of the microarray experiments. Therefore, although the 2.5-fold difference was selected as arbitrary, the up regulation of Cripto-1 in an art accepted model of human NeuroAIDS observed in the microarray experiments were not false positives but true positives and therefore demonstrate that up regulation of Cripto-1 beyond this level is a reliable indicator of NeuroAIDS." These arguments have been thoroughly reviewed but are not considered persuasive as the claims are not drawn to cripto-1, but SEQ ID NO 1. The specification has demonstrated that a nucleic acid that hybridizes to probes to SEQ ID NO 1 in macaque are over expressed in a pig tail macaque after SHIV infection. This does not indicate that SEQ ID NO 1 detects or is diagnostic of NeuroAIDS as SEQ ID NO 1 is not detected. Further the teachings of Williams suggest that neural tissue of pigtail macaque is not actively infected with SHIV.

The response has asserted the 2.5 fold greater increase in the nucleic acid that hybridized to probes to SEQ ID NO 1 were not false positives. The response has provided no evidence that the increased expression of the nucleic acid that hybridized to probes to SEQ ID NO 1 is anything more than normal variation in gene expression as described by Cheung and Wu.

The response again reiterates the arguments that macaque are a model of Neuroaids. This argument has been reviewed previously and is not considered persuasive.

The response on page 18 asserts, "Applicants reiterate (see the Berman declaration at ¶22) that the virus used in the studies of the instant application was SHIVs0oLNv (see the specification as filed, e.g., at ¶ [0075]), not SHIVKu2 (used in Raghaven (Raghaven at page 852, second column, first full paragraph) and discussed in Buch) or SIV. As stated above, SHIV is a better virus than SIV in producing a human model of NeuroAIDS. Also, the SHIV500LNv strain used in the instant application was shown to be activated in pig-tailed macaques (see Example 1 of the instant application). The differences seen in Raghaven are due to activation of the virus in rhesus macaque versus pig-tailed macaque. (Raghaven at page 856, second column, first full paragraph). Furthermore, Raghaven is silent as to whether the activation or non-activation of SHIV alters Cripto-1 expression. As stated in the previous response, non-activation of SHIV in pig-tailed macaque as described in Raghaven does not in itself foreclose the possibility of up regulation ofCripto-1. Indeed, the Applicants used a different viral strain that was activated in pig-tailed macaque and produces a better model of human NeuroAIDS due to this activation, which showed up regulation of Cripto-1. Therefore, one of ordinary skill in the art would have recognized that the methods as used by the Applicants would reliably report on up regulation of Cripto-1/SEQ ID NO: 1 in human NeuroAIDS. " The response asserts that the example 1 demonstrates that the SHIV500LNV virus is activated in the pig tailed macaques,

however example 1 merely indicates that brain had viral sequences, as did the pig-tailed macaques of Ragahavan. Thus the response has provided no evidence that SHIV500lvn is better than SHIVKU2 or that any pigtailed macaque, rhesus macaque, or human would with any type Neuroaids caused by any SHIV, SIV, or HIV infection could be diagnosed as having Neuroaids based on increased expression of SEQ ID NO 1.

The response continues by alleging the intra-species and interspecies variation of SEQ ID NO 1 up regulation is predictable for indicating NeuroAids. The response asserts that claims have been limited to humans and Macaque in order to advance prosecution. The response then agrees with the examiner that Roberts teaches proximity of neurons to damaging molecules plays a role in pathogenesis. The response continues, " However, this argument is of no moment in that the claims recite that up regulation of SEQ ID NO: 1 indicates NeuroAIDS. The claims state nothing regarding normal expression of or down regulation of SEQ ID NO: 1 or what this would indicate. There would have been no undue experimentation in determining whether SEQ ID NO: 1 is upregulated, as discussed throughout this response, and if SEQ ID NO: 1 is upregulated, this indicates NeuroAIDS." The response has apparently missed the point, that the claims are drawn to "any" central nervous system sample. Thus a sample from one region of the brain has unpredictable gene expression relative to another. The teachings of clearly indicate there is variability in the expression of "cripto1" in different regions of the brain in figure 2. Specifically control AX62 had the highest expression in PN or BG, while infected animal AX67 had no expression in BG and highest expression in HIP or MB, while CB4W appears to have similarly high levels

in TC, BG, HIP and MB, but no expression in CC. Thus the use of "any" central nervous system sample is not predictable as applicant's own data presented in post-filing art demonstrate variability in the "cripto1" gene across different regions of the brain.

The response again asserts that macaque is a model of neuroaids. These arguments have been previously addressed and are not persuasive for the reasons of record. the response continues, "However, one of ordinary skill in the art of human NeuroAIDS would have recognized that there are art accepted methods of compensating for these variations to provide animal models that reliably report on disease conditions in humans. The Applicants recognized that macaques are outbred and compensated by using a more stringent cut-off for the microarray experiments (specification as filed at ¶ [0073],), later confirmed by RT-PCR, as discussed above. Indeed, Roberts, as cited by the Examiner and as discussed above, uses a macaque NeuroAIDS model to report on conditions in human NeuroAIDS. Additionally, Chismar, published by the same laboratory as Roberts and discussed above, addresses the variation inherent in the methods as used by the Applicants and concludes that the approach is acceptable.' These arguments have been thoroughly reviewed but are not considered persuasive as Roberts uses 6 uninfected control samples. Chismar teachings are drawn to "calling of genes" between two species not the level of over expression as asserted. The response then asserts that Chismar cites Enard and recognizes the variation. While Chismar list Enard in the reference section the

examiner could find not reference to Chismar (or its reference number) in the text. These are arguments of counsel that have not been substantiated by evidence.

While the specification has provided evidence in the limited study performed that sequence that can hybridize to probes to SEQ ID NO 1 or primers that amplify sequences with homology to SEQ ID NO 1from pig-tailed macaque are increased relative to a single control animal it does not provide evidence the full breadth of the claims is enabled. Further, neither the specification nor the response have demonstrated that detection of a 2.5 or greater increased in expression of SEQ ID NO 1 is found in pigtail macaque and allows for detection of NeuroAids the claims are unpredictable, as SEQ ID NO 1 is not a macaque sequence. The response has asserted that the macaque is a good model of human NeuroAIDS, however the claims require detection of the increase allows for the detection of NeuroAIDS. Thus for the reasons set forth above the claims are not enabled.

Summary

NO claims are allowed.

Conclusions

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Steven C Pohnert/
Examiner, Art Unit 1634
Steven Pohnert